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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/823,712	SAgner
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 16, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *31-37* is/are allowed.

6) ☒ Claim(s) *1-14, 17-22, and 27-30* is/are rejected.

7) ☒ Claim(s) *15, 16, and 23-26* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *0503*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Specification

1. Claim 31 has been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-14, 17-22, and 27-30 are rejected under 35 U.S.C. 103(a) over Wittwer et al. (U.S. Patent 6,232,079 B1) (May 15, 2001) in view of Brown et al. (U.S. Patent 6,143, 496) (November 7, 2000).

Wittwer et al teach a method for determining the efficiency of the amplification ("Note that the amplification efficiency of the CTFR fragment appears greater than the neu fragment. The amplification efficiency can be rigorously determined by integrating the melting peak data as in example 16 (Column 41, last two sentences of the fourth paragraph)"of a target nucleic acid (Abstract, Column 13, line 65 to Column 14, line 32, and Figure 44 and Examples 7, 8, and 16) comprising the steps of:

b) the target nucleic acid is amplified under defined reaction conditions and the amplification is measured in real-time (Figure 44);

c) a defined signal threshold value is set (Figure 44);

d) determining the cycle number for each dilution at which the signal threshold value is exceeded (Figure 44 and Examples 7, 8, and 16));

e) determining a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded (clearly taught in Figures 15-17 and 42 and Column 33, line 10 to Column 34, line 52); and

f) calculating the amplification efficiency from the function determined in step e) (Figure 44 and Examples 7, 8, and 16).

Wittwer et al teach a method, wherein the amplification efficiency of a certain original amount of target nucleic acid is determined as the negative and reciprocal local first derivative of the continuously differentiable function (Figure 16 and Examples 7, 8, and 16).

Wittwer et al also teach a method for the absolute quantification of a target nucleic acid in a sample (Abstract and Column 12, line 43 to Column 13, line 64) comprising the steps of:

a) determination of the amplification efficiencies of the target nucleic acid and of an internal or external standard (Abstract and Example 16);

b) amplification of the target nucleic acid contained in the sample and of the standard under the same defined reaction conditions (Abstract and Example 16 and Figure 44);

c) measurement of the amplification of the target nucleic acid and standard in real time (Figure 44);

d) calculation of the original copy number in the sample with the aid of amplification efficiencies determined in step a) (Example 16 and Column 13, lines 29-45).

Wittwer et al. also teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from SybreGreen I (Example 14).

Wittwer et al. teach correction of copy number with the aid of amplification efficiencies (Example 16).

Wittwer et al clearly teach calculating the quotients of the function values (copy number) from the target nucleic acid and reference nucleic acid for the sample to be analyzed as well as for

the calibrator sample and determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample (Example 16 and Column 8, line 40 to Column 9, line 19).

Wittwer et al do not teach the preparation of different dilutions of the target nucleic acid.

Brown et al teach the preparation of a dilution of the target nucleic acid (Abstract, Example 1, Table 1 and Figure 8);

Wittwer et al do not teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from TaqMan probes.

Brown et al teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from TaqMan probes (Column 3, lines 25-59).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. since Brown et al state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state, "Thus, with rapid cycling the required times for amplification are reduced approximately 10-fold, and specificity is improved (Column 21, lines 1-3)". An ordinary practitioner would have been

motivated to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. in order to achieve the express advantages , as noted by Wittwer et al., of a method that allows rapid cycling by which the required times for amplification are reduced approximately 10-fold, and specificity is improved and also to achieve the express advantages, as noted by Brown et al., of a method for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process .

Allowable Subject Matter

4. Claims 15, 16, and 23-26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 31-37 are allowed.

Response to Amendment

5. In response to amendment, previous 112 (first paragraph) rejection has been withdrawn, thus rendering claims 31-37 allowable. However, 103 (a) rejection has been properly maintained.

Response to Arguments

6. Applicant's arguments filed on May 16, 2003 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually (page 19, second and third paragraph), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues (page 19, last paragraph to page 20, second paragraph) that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Brown et al as Brown et al. state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state,"Thus, with rapid cycling the required times for amplification are reduced approximately 10-fold, and specificity is improved (Column 21, lines 1-3)". An ordinary practitioner would have been motivated to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. in order to achieve the express advantages , as noted by Wittwer et al., of a method that allows rapid cycling by which the required times for amplification are reduced approximately 10-fold, and specificity is improved and also to achieve the express advantages, as noted by Brown et al., of a method for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process.

Applicant also argues (page 14, last paragraph to page 16, first paragraph and page 17, second and third paragraph) that Wittwer reference does not teach or suggest the main feature of the instant invention which is the determination of an amplification efficiency and determination of a cycle number at which amplification exceeds a threshold. These arguments are not persuasive. Wittwer et al. (U.S. Patent 6,232,079 B1) (May 15, 2001) clearly suggests amplification efficiency determination as specified above ("Note that the amplification efficiency of the CTFR fragment appears greater than the neu fragment. The amplification efficiency can be rigorously determined by integrating the melting peak data as in example 16 (Column 41, last two sentences of the fourth paragraph)". Moreover, Wittwer et al provides an equation (Column 33, lines 35-65) to calculate the efficiency of amplification reaction.

Applicant also argues (page 16, second paragraph) that Wittwer reference does not teach the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded. This argument is not persuasive. Wittwer clearly teaches the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded (clearly taught in Figures 15-17 and Figures 20-21 and 42 and Column 33, line 10 to Column 34, line 52).

Applicant then argues (page 16, second paragraph, last sentence) that the 103 rejection is improper because it is erroneous to rely on inherence to establish obviousness. This argument is

not persuasive because Wittwer clearly teaches the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded, as mentioned above and the word "inherently" has been withdrawn from rejection.

Applicant also argues (Page 21, second and third paragraph and Page 22, first paragraph) that neither Wittwer nor Brown reference teaches a reference nucleic acid standardized with a calibrator sample and the calculation of the ratio of target nucleic acid to reference nucleic acid. This argument is not persuasive. Brown clearly teaches a reference nucleic acid standardized with a calibrator sample and the calculation of the ratio of target nucleic acid to reference nucleic acid (Column 10, lines 30-50). Moreover, Wittwer et al. also clearly teach calculating the quotients of the function values (copy number) from the target nucleic acid and reference nucleic acid for the sample to be analyzed as well as for the calibrator sample and determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample (Example 16 and Column 8, line 40 to Column 9, line 19).

In view of the response to argument, all 103 (a) rejections are hereby being properly maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600is (703) 746-4979

Arun Chakrabarti

Patent Examiner

Art Unit 1634

June 9, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600